Research Article

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Microwave and Cs^+-assisted chemo selective reaction protocol for synthesizing 2-styryl quinoline biorelevant molecules

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Abstract: The reaction protocols and their continuous development to achieve the desired selectivity remain a primary target of organic chemistry, which is addressed here with the specific role of the cesium ion. The pharmacophore "2-styryl quinoline" was taken as a reference here because of the continuation of our work, where it was found fit as fusion inhibitors and anti-viral agents. The present protocol defines its importance for the synthesis of *O*-alkylated products. However, in most cases, *N*-alkylation proceeds because of nitrogen atoms' more nucleophilic nature and electronic density. The cesium effect makes this possible because of the large cationic size and its affection for the oxygen atom. The plausible mechanism and its progression were demonstrated here with the help of density function theory calculation by analyzing the energy of intermediates. The protocol is also found suitable with microwave irradiation. Moreover, it gives the product a better yield in less reaction time. The present reaction protocol and its importance will address some of the crucial issues related to the synthesis of the complex molecule, and the present protocol will open up hope, where the selectivity and product yield would be a concern.

Keywords: anti-viral, fusion inhibitors, cesium, *O*-selectivity, microwave irradiation, synthesis

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1 Introduction

Synthesis of the heterocyclic scaffold with ease has always been a challenge. However, many lucrative methods have evolved [1,2], but the synthesis or functionalization of the complex substrate is the most challenging task, a significant problem encountered with the region and chemo non-selectivity. The reaction with selectivity has always been a Herculean task concerning their region and stereo outcomes. Here we are developing a protocol for the selective *O*-alkylation over the *N*-alkylation, which is more prone to react because of its size and nucleophilicity [3]. The present protocol was developed using 2-styryl quinoline moiety, which was used as DNA binding [4], anticancer agents [5–10], and viral fusion inhibitors [11,12]. This activity makes the nucleus more valuable, and the reaction protocol gives direct value addition to the molecule through its selective substitution (Figure 1).

The 2-styryl quinolines are pharmacologically active molecules [13], reported with various other activities like anti-HIV-1 [14], antimicrobial[15], antimalarial [16], and anti-Alzheimer properties [17]. Some of the significant work on the 2-styryl quinoline was given attention for the drug discovery purpose. Among them, Chang et al. developed a series of styryl quinolines that were found to be effective anticancer agents [18]. Mrozek-Wilczkiewicz et al. demonstrated that styryl quinoline derivatives have significant anti-proliferative activity against human colon carcinoma cell lines [19]. El-Sayed et al. discovered a new class of 4,6-disubstituted 2-(4-(dimethylamino)styryl)quinolines with anticancer activity [8]. Mekouar et al. identified certain styryl quinoline compounds as a new class of powerful HIV-1 IN blockers that inhibited HIV replication *ex vivo* that were devoid of cytotoxicity at concentrations up to 100 mM [20]. Zouhiri et al. reported a number of new styryl quinoline analogues in order to investigate the SAR of inhibitors and show that the occurrence of a carboxyl group and a hydroxyl group at the C-7 and C-8 positions of the quinoline was needed for the drug's biological activity [21].

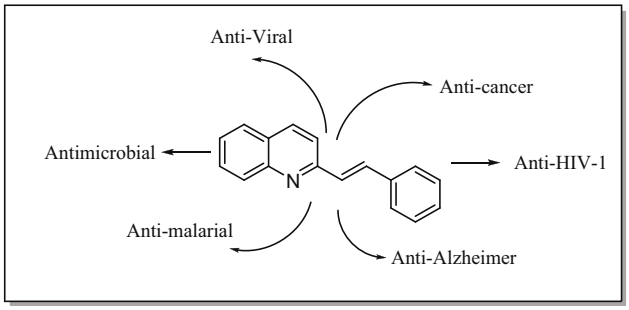


Figure 1: 2-Styryl quinoline pharmacophore and its pharmacological spectrum [8–21].

The search for the best fit molecule led us to the synthesis of 4-alkoxy quinoline derivatives (2) from the Quinolone (1) molecules through the alkylation reaction. However, some of the previously reported reactions were not favorable because of their selectivity over Nitrogen (N) and Oxygen (O) atom [22,23]. The nitrogen atom possesses more electronic density and is more prone to nucleophilic reaction toward electrophilic species (Figure 2).

Several reactions and conditions have been attempted with the conventional base like K_2CO_3 and NaOH to carry out the *O*-alkylation, but the result was not found to be satisfactory, as it is shown in the entries 2 and 3 of Table 1, the entire starting material was recovered; moreover, in entry 1, low yield (only 20%) was observed and the remaining starting materials were also recovered (Table 1, entries 1–3). However, the further use of cesium with the 1.5 and 3.5 equivalent amounts was satisfactory in the DMF solvent. The, microwave irradiation was found synergistic for improving the product yields. It was also observed that the Cesium ion (Cs^+) is also important for reaction in the microwave irradiation condition (Table 1, entry 7); however, the comparison with other carbonates also confirms the role of Cs^+ (Table 2). The high yield and selective reaction protocol with lesser time make this reaction greener with multiple advantages.

The effect of Cs^+ signifies the importance of the *O*-alkylation with the high level of selectivity. Compared to other cations, the large cationic radius of the ions makes the Cs^+ naked and reactive in the non-polar solvents.

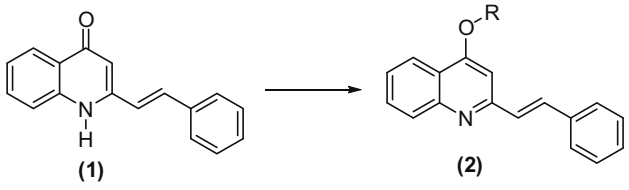


Figure 2: *O*-Alkylation of the 2-styryl quinolone [8–12].

Table 1: Reaction conditions for *O*-alkylation of (*E*)-2-styryl quinoline-4-ol

S. No.	Reagents	Conditions	Yields (%)
1.	K_2CO_3, DMF	80°C, 12 h	20
2.	NaH, THF	RT, 12 h	No product
3.	NaOH NaH, DMF	RT, 12 h	No product
4.	Cs_2CO_3 (1.5 equiv.), DMF	RT, 24 h	20
5.	Cs_2CO_3 (3.5 equiv.), DMF	80°C, 3.5 h	57–74[a]
6.	Cs_2CO_3 (1.5 equiv.), DMF	MW, 15 min	60–78
7.	DMF	MW, 15 min	0[b]

[a]varied depending upon alkyl chain, [b]starting material was recovered.

The solvent optimization study was also done with various non-polar solvents like dimethyl sulfoxide (DMSO), *N*-Methyl-2-pyrrolidone (NMP), and dimethylacetamide (DMP), but the role of the polar aprotic was found similar in all the aprotic solvents. The choice of the solvent was done based on the rate and boiling point of the solvents and the DMF was kept constant for further optimization of the substrate scope. The role of Cs^+ shows selectivity because of its not too strong and too weak character. Various reported experiments also define the unique role of Cs^+ in the aprotic solvents, with their cationic character, to develop a selective protocol [24,25]. To find the reaction mechanism, the energy minimization process was done with the density function theory (DFT) calculation protocol described in Section 2.

2 Experimental method (DFT)

Gaussian 16 package was used to perform all the calculations utilizing DFT-based methodologies. The ground state was optimized using various methods such as B3LYP,

Table 2: Optimization of the reaction condition using other carbonate base

S. No.	Reagents	Conditions	Yields[a] (%)
1.	Cs_2CO_3 (1.5 equiv.), DMF	MW, 15 min	74
2.	Li_2CO_3 (1.5 equiv.), DMF	MW, 15 min	0[b]
3.	K_2CO_3 (1.5 equiv.), DMF	MW, 15 min	0[b]
4.	Na_2CO_3 (1.5 equiv.), DMF	MW, 15 min	0[b]

[a]Yield calculated after chromatographic isolation; [b]starting material were recovered.

LSDA, and B3PW91, along with the 6-311 + G(d,p) basis set. HOMO and LUMO energy values were used to calculate the variety of global reactivity descriptors and defined as follows [26]:

$$\chi(\text{electronegativity}) = -\frac{1}{2}(E_{\text{HOMO}} + E_{\text{LUMO}}),$$

$$\mu(\text{chemical potential}) = -\chi,$$

$$\eta(\text{chemical hardness}) = \frac{1}{2}(E_{\text{LOMO}} - E_{\text{HOMO}}),$$

$$S(\text{chemical softness}) = \frac{1}{2}\eta,$$

$$\omega(\text{electrophilicity index}) = \frac{\mu^2}{2\eta}.$$

2.1 DFT

In order to find out the geometry and to calculate the variety of parameters such as chemical reactivity, kinetic stability, and optoelectronic attributes of a molecule, DFT-based methods have been used. First, to assess the computational cost and reliability, prescreening was carried out by utilizing various DFT-based methods. From the observation, it was observed that B3LYP/6-311 + G(d,p) is the perfect method based on correlation derived from zero point energy. After that, to explore the titled compound's electrostatic parameters, the energy of HOMO and LUMO in the gas phase was calculated utilizing the B3LYP/6-311 + G(d,p) level of theory as frontier molecular orbitals play a significant role in determining the wide range of intermolecular interactions present within the molecule. The molecular stability and chemical and spectro-chemical properties of a molecule can be assessed by the energy gap between HOMO and LUMO. As can be seen from Figure 3, HOMO and LUMO are found to be localized on the 2-styryl quinoline ring. The energy difference between HOMO and LUMO was found to be 3.908 eV which revealed the high stability of the molecule. The concept of chemical potential, which defines a molecule's electron donating and withdrawing capacity. The greater the potential chemical values, the higher the molecules' tendency to donate electrons. Chemical hardness describes the capability of the molecule to withstand the alteration in electron density. The more significant energy difference between HOMO and LUMO leads to harder molecules and high stability. The electrophilicity index (ω) tells us about the energy of stabilization of the molecule after accepting an electron; the lower the value of the electrophilicity index, the better the nucleophilicity of the molecule. The range of

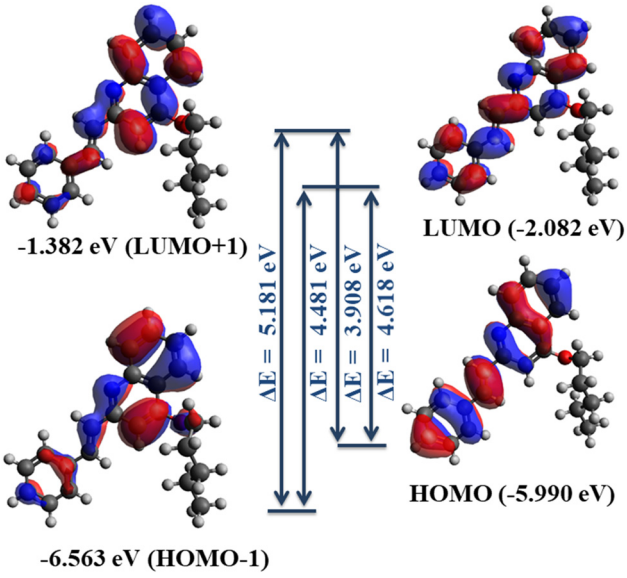


Figure 3: Molecular orbital diagram for 2a.

global reactivity parameters such as chemical potential and softness, chemical hardness, and electronegativity was calculated using the HOMO-LUMO energy difference outlined in Table 3.

2.2 MM2 energy calculation through Gaussian 16

The mechanism of the reaction was carried out, and the energy calculation of the compounds and its intermediate study suggest the thermodynamic pattern and the energy study claims that the *O*-alkylation and the Cs$^+$-based intermediate also confirm that the positive process through the attachment of Cs$^+$ to oxygen makes this reaction possible. The energy of the *O*-alkylated product and its Cs$^+$ abduct its thermodynamic behaviors and process probability to get the *O*-alkylated products over the *N*-alkylation (which has high energy) (Figure 4).

The plausible mechanism or role of the Cs$^+$ was depicted through the below mechanistic representation, with the HOMO–LUMO energy calculation of the compounds **2d** and **3a** where the R corresponds to the ethyl groups. The energy of the compounds **2d** and **3a** is 13.96 and 39.17 kcal/mol, respectively, which clearly shows that compound **2d** has the possibility of formation through thermodynamics, which is more stable. Moreover, the HOMO-LUMO energy gap of compound **2d is** 3.9 eV and **3a** is 4.2 eV, which also confirms the possibility of the formation of the compound 2d instead of **3a** (Figure 5).

Table 3: Calculated energy and global descriptors

Compounds	HOMO (eV)	LUMO (eV)	Chemical hardness (μ)	Global hardness, $\eta = -\mu$	Global electrophilicity index, $\omega = \mu^2/2\eta$	Softness, $s = 1/\eta$
2a	−5.990	−2.082	−4.036	4.036	2.018	0.248
2b	−5.993	−2.085	−4.039	4.039	2.020	0.248
2c	−5.979	−2.070	−4.025	4.025	2.012	0.248
2d	−5.907	−1.986	−3.947	3.947	1.973	0.253
2e	−5.909	−1.988	−3.949	3.949	1.974	0.253
2f	−5.985	−2.080	−4.033	4.033	2.016	0.248
2g	−5.502	−2.062	−3.782	3.782	1.891	0.264
2h	−5.961	−2.044	−4.003	4.003	2.001	0.250
2i	−5.883	−1.965	−3.924	3.924	1.962	0.255

The mechanism of the formation of compound **2d** claims that the initiation of reaction starts with the attraction of the oxygen atom and Cs^+ because of its well-established affection toward the oxygen atom. The attraction and the ionic bond are compensated with the response from the non-bonding electron of the nitrogen, which makes the reaction feasible from the oxygen side. The reaction ends with the stabilization of the charge with a unique *O*-alkylated product, which is also justified by the DFT calculation [23,27].

The optimized reaction condition was found to use Cs_2CO_3 (3.5 equiv.) in DMF for 15–20 min in microwave irradiation conditions for the synthesis of *O*-4-alkyl derivatives of 2-styryl quinoline based on the strategy shown in Scheme 1. As a result, a series of eight new *O*-4-alkylated derivatives were synthesized by the modification of the hydroxyl group present at the four positions of the 2-styryl quinoline ring with a wide range of substituents such as ethyl, propyl, butyl, isopropyl, isobutyl, neopentyl, allyl, etc. In addition, the pharmacophore confirmed the

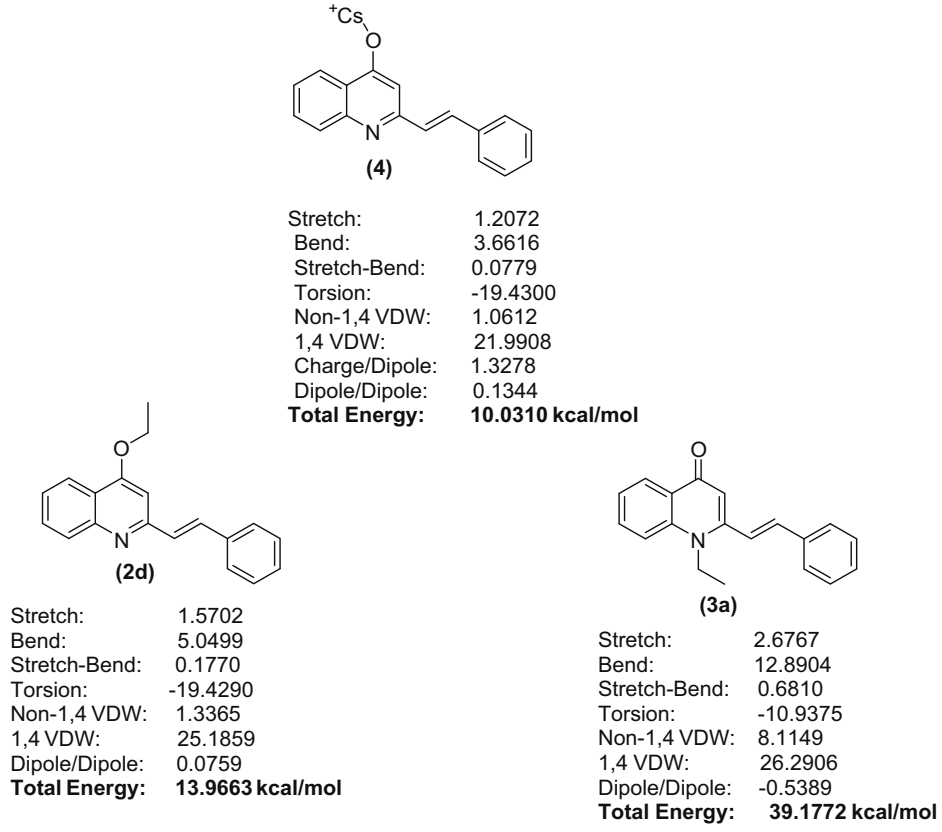


Figure 4: Energy of intermediate and the product.

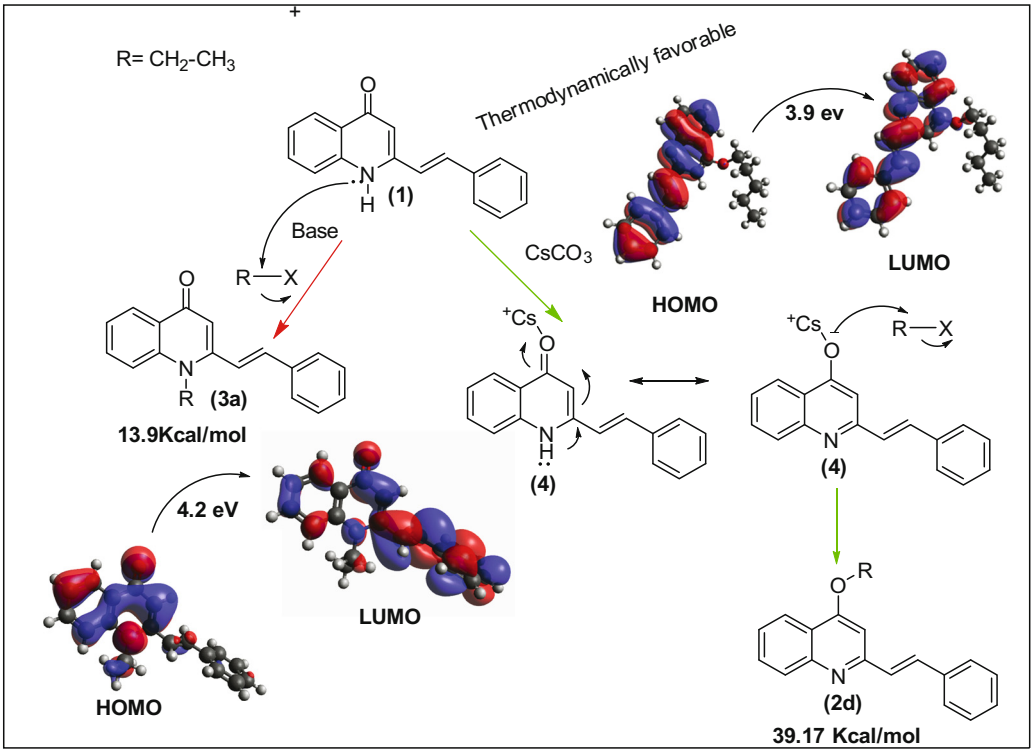
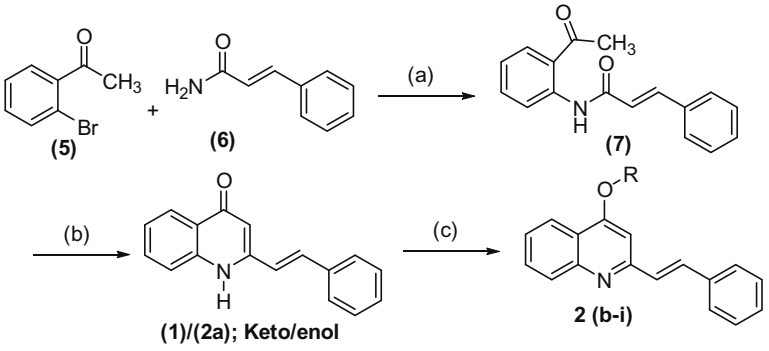


Figure 5: Plausible mechanism of the *O*-alkylation.



2a: R= -H, 74%
2b: R= -$CH_2CH_2CH_2CH_3$, 58%
2c: R= -$CH_2CH_2CH_2CH_2CH_3$, 57%
2d: R= -CH_2CH_3, 65%
2e: R= -$CH(CH_3)_2$, 63%
2f: R= -$CH_2CH_2CH_3$, 69%
2g: R= -$CH_2C(CH_3)_3$ 65%
2h: R= -$CH_2CH{=}CH_2$, 74%
2i: R= -$CH_2CH(CH_3)_2$, 58%

Reagents and conditions: (a) *N*, *N*'-dimethylethylene diamine, K_2CO_3, CuI, toluene, 110 °C, 25 h, 61% (b) NaOH, dioxane, 90 °C, 3 h, 74% (c) alkyl halide, Cs_2CO_3, DMF, 80 °C, 3.5 h, 57-74%

Scheme 1: Synthesis of 4-substituted 2-styryl quinoline derivatives (**2a–i**).

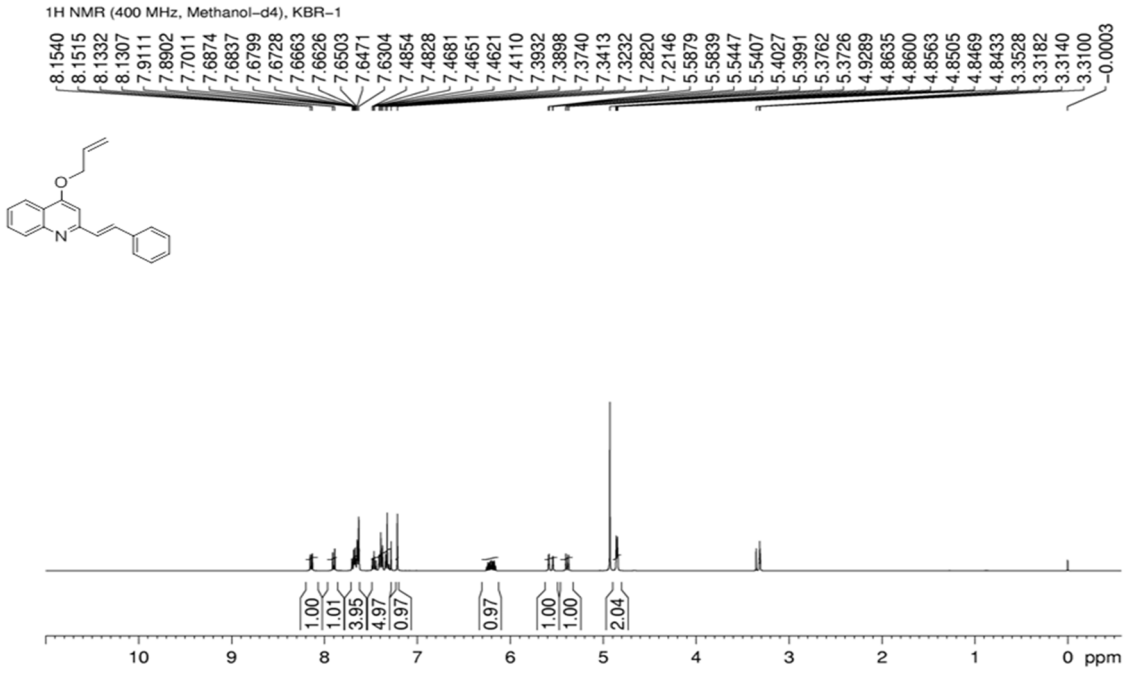


Figure 6: ^{1}H NMR spectrum of compound **2h** in methanol-d_4.

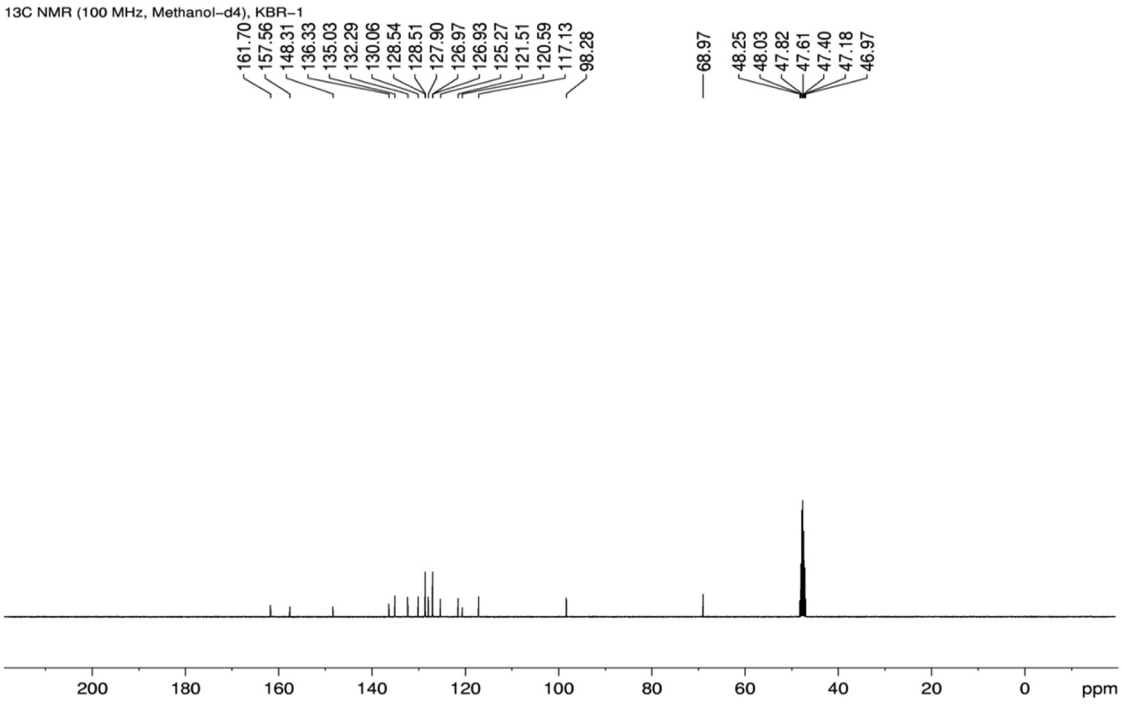


Figure 7: ^{13}C NMR spectrum of compound **2h** in methanol-d_4.

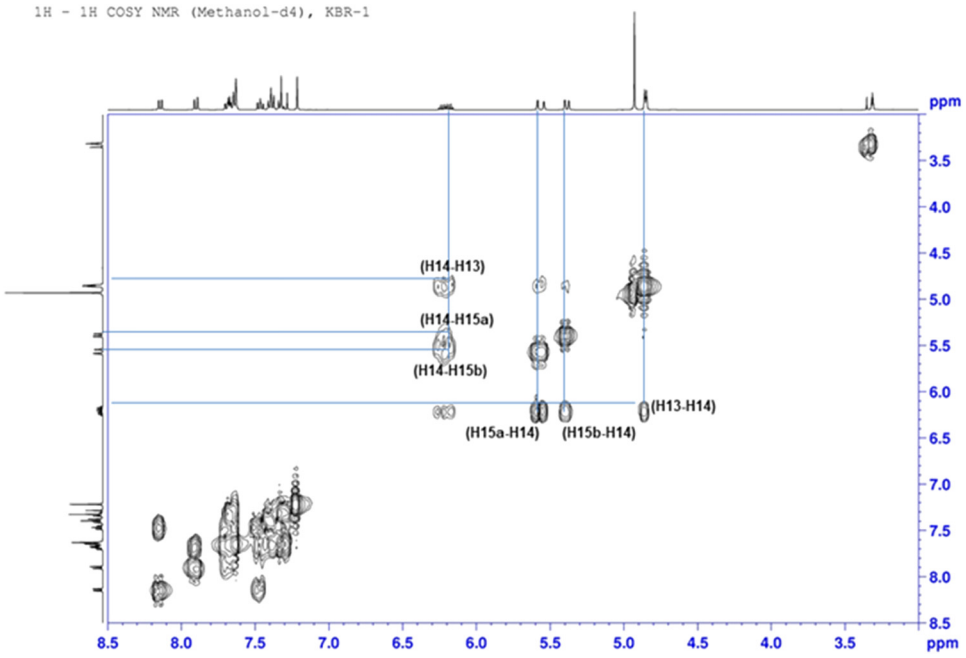


Figure 8: ^{1}H–^{1}H COSY spectrum of compound **2h** in methanol-d_4.

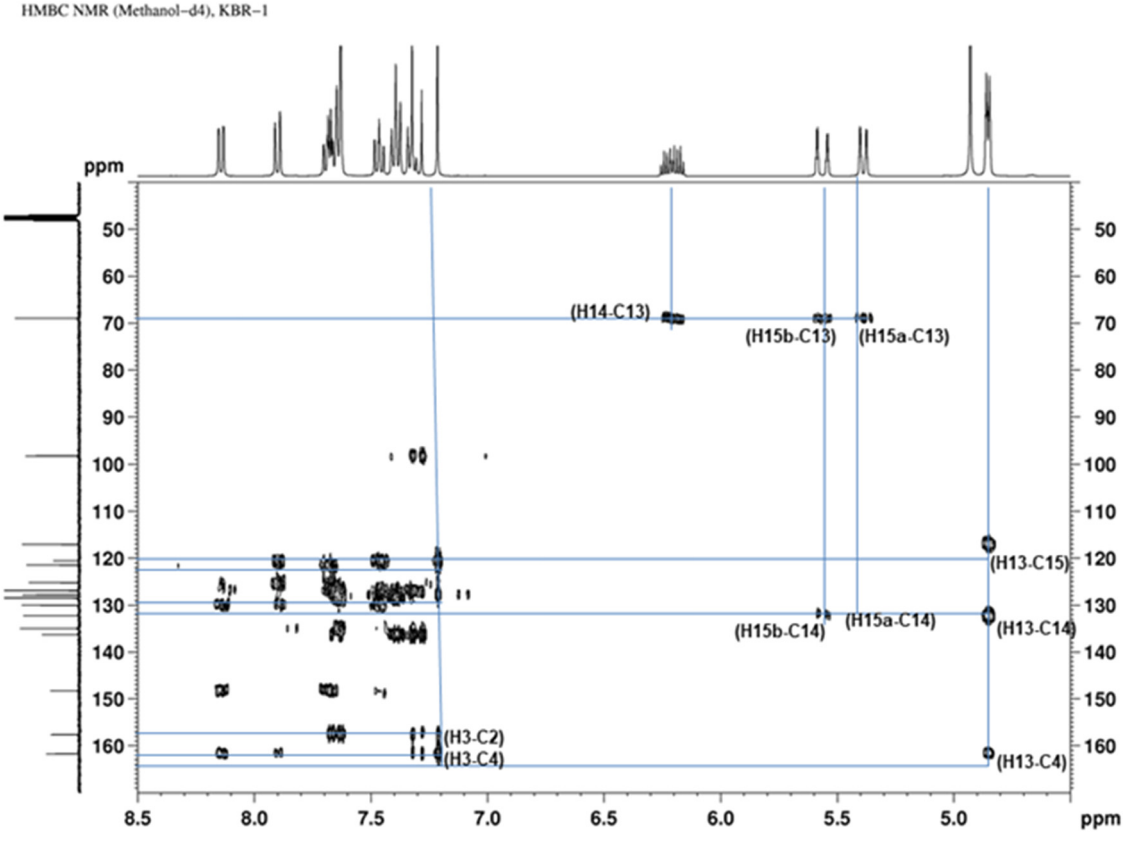


Figure 9: ^{1}H–^{1}H HMBC spectrum of compound **2h** in methanol-d_4.

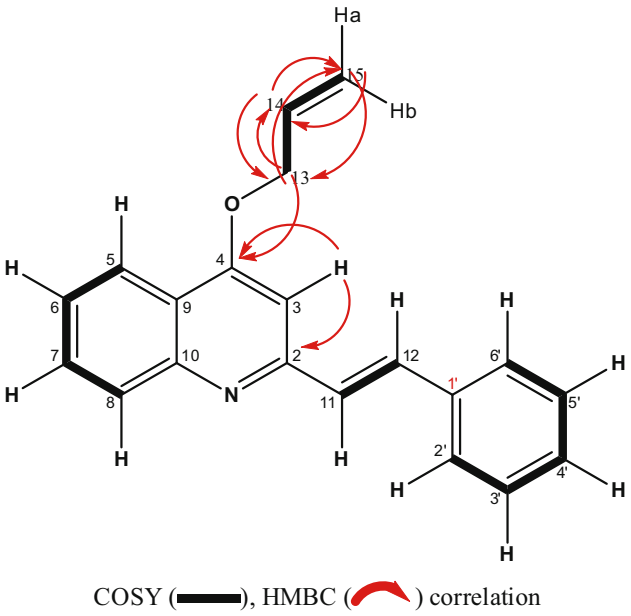


Figure 10: Structure elucidation of compound **2h**.

broad spectrum anti-viral activity because of their reported affinity towards the spike protein.

3 Discussion

All the newly synthesized compounds were characterized using HRMS, ^{1}H NMR, ^{13}C NMR, IR, and melting point. The formula for compound **2h** was established as $C_{20}H_{17}NO$. Based on ESI-HRMS data *m/z* found 310.1204 $[M + Na]^{+}$ (calcd *m/z* 310.1202 for $[M + Na]^{+}$). In the IR spectrum, the signal at 1,100 cm^{-1} revealed the presence of olefin.

Combined analysis of the ^{1}H NMR (Figure 6) and ^{13}C NMR (Figure 7) spectroscopy data revealed the presence of 10 protons in the aromatic region, 20 carbons in the range of δ value of 161–68 ppm, and 1 carbon at the δ value of 68.96, 98.27, 117.12, 120.58, 121.51, 125.27, 126.92, 126.97, 127.89, 128.50, 128.53, 130.06, 132.28, 135.02, 136.33, 148.31, 157.56, 161.69 ppm. The ^{1}H–^{1}H COSY correlations H-13 with H-14, H-14 with H-13, H-15a, and H-15b, and H-15a with H-14 and H-15b showed the connectivity of adjacent protons (Figure 8). In the HMBC spectrum, H-3 was correlated with carbon at δ 161.69 (C-4) and 157.56 (C-2). H-13 was correlated with carbon at δ 161.69 (C-4), 132.28 (C-14), and 117.12 (C-15), while H-14 was correlated with carbon at δ 68.96 (C-13). H-15 was correlated with carbon at δ 68.96 (C) and 132.2 (C-14) (Figure 9).

The HMBC experiment confirmed alkylation at the 4-OH position; in the case of compound **2h**, methylene proton (δ 4.84) of allyl moiety attached at 4-OH of (*E*)-2-styryl quinoline-4-ol showed a correlation with carbon at 4-position (δ 161.69) as depicted in Figure 10.

4 Conclusion

Quinoline scaffold is widely present in several natural and synthetic molecules. The molecules containing this scaffold have different pharmacological activities explored to obtain potent anti-viral and anti-cancer activity. A series of 25 new *O*-4-alkylated styryl quinoline derivatives were synthesized by modification of the hydroxyl group present at the 4 positions of the 2-styryl quinoline ring with a wide range of alkyl substituents using cesium carbonate as base and DMF as solvent at 80°C for 3.5 h, which were found to be the optimum reaction condition for *O*-4 alkylation of 2-styryl quinoline. Furthermore, the reaction was claimed to be greener because of its suitability in microwave irradiation conditions. The synthesis of these compounds with high selectivity can be helpful in the future HTS screening of compounds for a suitable target.

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Author contributions: Ravi Kumar Mittal: synthesis, characterization, and software; Priyank Purohit: methodology, investigation, and writing the draft; Magda H. Abdellattif: funding acquisition, software, and final editing; Meenu Aggarwal: instrumentation, project administration, and software.

Conflict of interest: The authors declare that there is no conflict of interest.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: All data generated or analyzed during this study are included in this published article.

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